REMARKS

Claims 1, 3, 7-20, 22, and 37 are pending in the application. Claim 1 has been amended. Support for the amendments can be found in the specification at, e.g., page 5, lines 17-29; page 13, lines 6-13; page 14, lines 11-20; and page 16, lines 4-8. These amendments add no new matter.

35 U.S.C. § 103(a)

On pages 2-6 of the Office Action, claims 1, 3, 7, 9, 12, 13, 15, 17-19, and 37 were finally rejected as allegedly unpatentable over Cordell et al., WO 91/04339 ("Cordell"), Hitzeman et al., U.S. Patent No. 4,775,622 ("Hitzeman"), and Chang et al., U.S. Patent No. 5,010,003 ("Chang").

Applicant respectfully traverses the rejection in view of the claim amendments and the following comments.

Independent claim 1, as amended, is directed to a method of identifying a candidate substance that inhibits aggregation of a mammalian aggregate-prone amyloid protein in a yeast cell. The claimed method includes the following steps: (a) contacting a yeast cell that expresses a chimeric aggregate-prone amyloid protein comprising a mammalian aggregate-prone amyloid peptide with a candidate substance under conditions effective to allow aggregated amyloid formation in the yeast cell; and (b) determining the ability of the candidate substance to inhibit the aggregation of the aggregate-prone amyloid protein in the yeast cell.

The Office Action interpreted the previously pending version of claim 1 as not requiring that the steps of the claimed method be carried out in a yeast cell. The present amendment makes explicit that the aggregation (and inhibition thereof by a candidate substance) of a mammalian aggregate-prone amyloid protein takes place in a yeast cell.

Cordell describes methods of screening to identify agents that can reduce preamyloid aggregate formation. However, Cordell does not describe an assay that uses a yeast host cell expressing a chimeric aggregate-prone amyloid protein comprising a mammalian aggregate-prone amyloid peptide to evaluate candidate substances for their ability to inhibit the aggregation of the aggregate-prone amyloid protein.

Hitzeman and Chang do not add what is lacking in Cordell. Hitzeman describes transformation of yeast with an expression vector encoding a polypeptide containing a signal sequence and a heterologous protein, such that the signal sequence results in secretion of the heterologous protein from the yeast. Chang also describes methods of secreting a heterologous protein from yeast.

Consistent with the preceding comments regarding the secretion of proteins from yeast, the Office Action stated that Chang and Hitzeman described "the advantages of high level expression, processing and secretion of heterologous proteins into yeast media." In addition, the Office Action stated that "testing may occur following purification of peptide without the further necessity of cell lysis and potential contamination by alternative immature forms of the peptide." The Office Action asserted that the combination of Cordell, Hitzeman, and Chang would result in an assay conducted on a protein secreted from yeast into cell culture media.

In contrast to the assay resulting from combination of references proposed in the Office Action, claim 1 requires that the method be carried out in a yeast cell (i.e., not using a secreted protein) under conditions effective to allow aggregated amyloid formation of the chimeric aggregate-prone amyloid protein. It is under these conditions that, according to claim 1, a candidate substance is evaluated for it ability to inhibit the aggregation of the aggregate-prone amyloid protein in the yeast cell. Because the method that results from the Office Action's suggested combination of references is not carried out in a yeast cell as is required by claim 1, the combination of the cited references necessarily fails to suggest the method of claim 1.

In addition to comments regarding the alleged obviousness of an assay conducted on a protein secreted from yeast into cell culture media, the Office Action also stated that

> [n]evertheless, this does not preclude that the expression of the proteins involves an intracellular phase where the protein may be contacted while inside the cell and prior to secretion. Accordingly the limitations are met and the combination as suggested arrives at the claimed invention.

As noted above, Hitzeman and Chang describe the secretion of proteins from yeast. Because the proteins of Hitzeman and Chang are described as being secreted, the skilled person would have had no reason to expect that yeast that produce such secreted proteins could or should be used to evaluate aggregation of the proteins within the cell. There is no evidence of

record to suggest that such an aggregation event would occur or that the skilled person, at the time the present application was filed, would have had any reason to screen for aggregation (in a yeast cell) of a protein that contains a sequence intended to cause its secretion. For a finding of obviousness, both a teaching or suggestion to make the claimed combination as well as a reasonable expectation of success must be found in the prior art. MPEP § 706.02(j). The cited references provide neither the requisite teaching or suggestion nor a reasonable expectation of success.

In light of these comments, applicant respectfully submits that the combination of Cordell, Hitzeman, and Chang does not render the claimed invention obvious and therefore request that the Examiner withdraw the rejection of independent claim 1 and dependent claims 3, 7, 9, 12, 13, 15, 17-19, and 37.

On pages 6-9 of the Office Action, dependent claims 8, 17, 18, and 20 were finally rejected as allegedly unpatentable over Cordell, Hitzeman, and Chang as set forth above and further in view of Chalfie et al. (1994) Science 263:802-05 ("Chalfie").

The Office Action cited Chalfie as allegedly describing the use of green fluorescent protein as a marker for gene expression and asserted that the skilled artisan would have been motivated to use green fluorescent protein to monitor protein aggregation in yeast cell culture media.

As detailed above, the combination of Cordell, Hitzeman, and Chang suggested by the Office Action would result in an assay conducted on a protein secreted into cell culture media, rather than an assay carried out in a yeast cell as is required by claim 1. Chalfie provides nothing that supplements the deficiencies of Cordell, Hitzeman, and Chang or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, dependent claims 8, 17, 18, and 20 should also be in condition for allowance.

On pages 9-11 of the Office Action, dependent claims 7, 10, and 11 were finally rejected as allegedly unpatentable over Cordell, Hitzeman, and Chang as set forth above and further in view of Tikhonenko et al. (1995) Oncogene 11:1499-508 ("Tikhonenko").

The Office Action cited Tikhonenko as allegedly describing the use of the glucocorticoid receptor element as a marker for protein inducible expression and asserted that the skilled artisan would have been motivated to modify the fusion proteins of Cordell to use the glucocorticoid receptor to monitor and induce protein expression in a cell culture assay.

As detailed above, the combination of Cordell, Hitzeman, and Chang suggested by the Office Action would result in an assay conducted on a protein secreted into cell culture media, rather than an assay carried out in a yeast cell as is required by claim 1. Tikhonenko provides nothing that supplements the deficiencies of Cordell, Hitzeman, and Chang or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, dependent claims 7, 10, and 11 should also be in condition for allowance.

On pages 11-13 of the Office Action, dependent claim 16 was finally rejected as allegedly unpatentable over Cordell, Hitzeman, and Chang as set forth above and further in view of Nordstedt et al. (1994) J. Biol. Chem. 49:30773-76 ("Nordstedt").

The Office Action cited Nordstedt as allegedly teaching that the Abeta peptide develops protease resistance in association with its polymerization into amyloid fibrils. The Examiner asserted that the skilled artisan would have been motivated to modify the methods of Cordell to determine the ability of a candidate substance to inhibit aggregation by assessing the aggregate-prone amyloid protein aggregation as detected by increased protease resistance.

As detailed above, the combination of Cordell, Hitzeman, and Chang suggested by the Office Action would result in an assay conducted on a protein secreted into cell culture media, rather than an assay carried out in a yeast cell as is required by claim 1. Nordstedt provides nothing that supplements the deficiencies of Cordell, Hitzeman, and Chang or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, dependent claim 16 should also be in condition for allowance.

On pages 13-17 of the Office Action, dependent claims 14 and 22 were finally rejected as allegedly unpatentable over Cordell, Hitzeman, and Chang as set forth above and further in view of Patino et al. (1996) Science 273:622-26 ("Patino").

The Office Action cited Patino as allegedly describing Sup35 as a yeast homologue of prion protein and Hsp104 overexpression in yeast cells as capable of converting Sup35 from an aggregating form to a non-aggregating form.

As detailed above, the combination of Cordell, Hitzeman, and Chang suggested by the Office Action would result in an assay conducted on a protein secreted into cell culture media, rather than an assay carried out in a yeast cell as is required by claim 1. Patino provides nothing that supplements the deficiencies of Cordell, Hitzeman, and Chang or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, dependent claims 14 and 22 should also be in condition for allowance.

CONCLUSIONS

Applicant submits that all grounds for rejection have been overcome, and that all claims are in condition for allowance, which action is requested.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 17481-004001.

Respectfully submitted,

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